Is there an association between socioeconomic status and immune response to infant and childhood vaccination in the Netherlands?

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ABSTRACT

Introduction

Socioeconomic status (SES) is a well-known determinant of health, but its relation with vaccine-induced immunity is less documented. We explored the association between SES and immunoglobulin G (IgG) levels against vaccine-preventable diseases in vaccinated children in the Dutch National Immunization Programme.

Methods

Data from a population-wide cross-sectional serosurvey in the Netherlands (2006-2007) were used. We compared geometric mean IgG concentrations/titers (GMC/T ratios) against measles, mumps, rubella, *Haemophilus influenzae* type b (Hib), *Neisseria meningococcus* type C, diphtheria, tetanus, poliovirus types 1,2,3 and pertussis in children of high versus low SES by linear regression analysis. We included 894 children (0-12 years) at one of two timeframes: 1 month to 1 year, or 1-3 years after vaccination. Mother's educational level and net household income served as binary indicators of SES.

Results

Of 58 possible associations of vaccine-induced antibody responses with educational level and 58 with income, 10 (9%) were statistically significant: 2 favouring (that is, with higher IgG levels at) high educational level (for Hib 1m-1y after vaccination (GMC/T ratio: 2.99, 95%CI: 1.42-6.30)

and polio 2 1m-1y after the 9-year booster dose (1.14, 1.01-1.27)) and 8 favouring low income (polio 1, 2 and 3 1m-1y after the 11-month booster (0.74, 0.58-0.94; 0.79, 0.64-0.97; 0.72, 0.55-0.95), polio 3 and pertussis 1-3y after the 11-month booster (0.70, 0.56-0.88; pertussis-prn: 0.60, 0.37-0.98; pertussis-ptx: 0.66, 0.47-0.95), mumps and rubella 1-3y after first vaccination (0.73, 0.55-0.97; 0.70, 0.55-0.90), and rubella 1m-1y after second vaccination (0.83, 0.55-0.90)). After adjustment for multiple testing, none of the differences remained significant. There was no association between SES and proportion of children with protective IgG levels.

Conclusion

In this explorative study, we found no consistent association between SES and immune response to vaccination in the Netherlands and no association with protective IgG levels. Additional studies in other settings should confirm this finding.

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INTRODUCTION

Socioeconomic status (SES) is a well-known determinant of health [1]. It is a multi-faceted phenomenon that is at least partly captured by parameters such as education, occupational class and income. People with higher educational levels, from higher occupational classes and with higher income tend to have better health outcomes, although true causality is difficult to prove [2].

The association between SES and non-communicable diseases has been studied extensively [3], but less is known about the effect of socioeconomic status on acute infectious diseases, except for its relation with the risk of exposure (e.g. crowding) and with vaccination coverage [4,5]. In a recent study in the Netherlands, some differences in the incidence of self-reported, common infectious disease syndromes (acute upper and lower respiratory tract infections, acute otitis media and urinary tract infections) were found between people from high versus low educational level, but they were not consistently in favour of either high or low educational level [6].

Exposure to stress of various nature early in life has been shown to programme the immune system [7]. Environmental factors, including exposure to pathogens, but also psychological stress, poor nutrition and smoking are thought to affect one's immune response although it is not known to what extent [8,9]. The effect of SES on immunoglobulin-G (IgG) levels after natural exposure was shown to be pathogen specific and not consistently pointing to one direction in a recent study among adults [10]. To study the effect of SES on immune response independently of its association with exposure, one could compare the immune response to (childhood) vaccination, particularly against diseases that are no longer endemic in the area, between low and high SES groups. Hence, exploring the relation between SES and immune response to vaccination provides additional insights that could help to disentangle the complex interaction between SES and communicable diseases. Moreover, it might be a first step towards optimizing protection against vaccine preventable diseases in future. The aim of this study was to explore the possible association of mother's educational level and net household income (as proxy indicators of SES) with immune response to vaccination in infants and children vaccinated according to the National Immunization Programme (NIP) in the Netherlands.

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METHODS

Study population

We used data from a population-wide cross-sectional serosurvey (the Pienter2 study) that was conducted in the Netherlands between February 2006 and June 2007. The aim of the Pienter2 study was to establish a national serum bank to monitor antibody levels against vaccine-preventable infectious diseases in the NIP [11]. For sampling in Pienter2, the Netherlands was divided in five regions and participants (0-79 years) were chosen from eight randomly selected municipalities in each region. People who agreed to participate, were asked to complete a questionnaire with questions on their background, immunisation status and health, and to donate a blood sample. For children younger than 14 years, a parent or guardian was asked to fill the questionnaire. In total, 19,781 people were invited to participate in Pienter2 which resulted in 6,348 (32%) completed questionnaires with supplementary blood samples, including an oversampling of non-Western migrants. The study was approved by the Medical Ethics Committee of the foundation of therapeutic evaluation of medicines (METC-STEG) in Almere (The Netherlands) [11].

For our study, only children from Pienter2 who were immunized according to the NIP were included. At the time of the study, the NIP included DTaP-IPV-Hib (Diphtheria, Tetanus, Pertussis, inactivated Poliovirus and *Haemophilus influenza* type b) infant vaccinations at 2, 3, 4 and 11 months (up to 1999 at 3, 4, 5 and 11 months; Hib included since 1993), and childhood booster vaccinations at 4 and 9 years of age for DT-IPV (since 1962). Since 2001, the booster vaccination at 4 years covers pertussis as well. From 2005 onwards, the pertussis component in the DTP-IPV vaccine was changed from whole cell to acellular. The NIP also includes a MMR (measles, mumps, rubella) vaccine at the age of 14 months and 9 years. The MMR vaccine at 14 months is combined with MenC vaccination (since 2002). Vaccination coverage at the age of two years was 94.3% and 94.0% in respectively 2006 and 2007 for DTP-IPV, 95.4% and 95.0% for Hib, 94.8% and 95.6% for MenC and 95.4% and 95.9% for MMR. At the age of 10 years, vaccination coverage for DT-IPV was 93.0% and 92.5% and for MMR 92.9% and 92.5% [12]. Dates of vaccination were copied from the vaccination booklet that participants had to bring to the visit where the blood sample was collected, and checked afterwards in the digital national immunization register. We only included children whose blood sample was taken between 1 month and 1 year (short-term) or between 1 and 3 years (medium-term) after infant vaccination (that is, primary series + booster dose at 11 months of DTP-IPV and Hib; first MMR and MenC at 14 months), or childhood vaccination (that is, booster dose of DT-IPV or DTP-IPV at 4 years;

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booster dose of DT-IPV at 9 years; second MMR at 9 years). Furthermore, to be included in the study, the age range within which vaccination had to be received, was 10-14 months for the first booster vaccination of DTP-IPV (DTP-IPV4 scheduled at 11 months of age), 13-17 months for MMR1, 42-60 months for the 4-year booster vaccination of DT(P)-IPV, and 96-120 months for the 9-year booster of DT-IPV and MMR2. We excluded infants and children who reported to have been diagnosed with clinical pertussis or mumps.

Indicators of SES

We used educational level of the mother and net household income as two separate indicators of SES, since this information was requested in the Pienter2 questionnaire. Children of whom no information was available on one of these indicators, were excluded from analysis with that indicator. To be able to include a sufficient number of children in each stratum, the indicators of SES were used in a binary way: low-intermediate educational level (no education, primary education, junior technical school, or lower general or intermediate vocational secondary education) versus high educational level (higher vocational or higher general secondary education, pre-university or university education), and low-intermediate net household income (≤ € 3,050/month) versus high net household income (> € 3,050/month).

We repeated the analysis with a subset of children who belonged to the “low/intermediate-category” for both educational level of the mother and net household income versus children who belonged to the “high-category” for both SES indicators to compare the extremes in a joint effect of educational level and household income.

Laboratory analysis

In the Pienter2 survey, IgG levels were determined by a fluorescent bead-based multiplex immunoassay (MMRV-MIA) using Luminex for simultaneous detection of antibodies against measles, mumps and rubella [13]. Antibodies against MenC and Hib were measured in a similar way, using combined assays [14]. Pentaplex MIA was used to determine IgG levels against pertussis (pertussis toxin (ptx), pertactin (prn) and filamentous hemagglutinin (FHA)), diphtheria, and tetanus [15]. Polio IgG total antibody levels (against poliovirus types 1, 2, and 3) were measured with a standard neutralization test [16]. The IgG concentrations were determined and calibrated to internationally accepted standards, such as the cut-off criteria of the World Health Organization (WHO).

Data analysis

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We described the study population included after infant and childhood vaccination with descriptive statistics. We calculated geometric mean IgG titers/concentrations (GMC/T; with 95% confidence intervals) for each pathogen at the two timeframes (1 month-1 year and 1-3 years) after infant and childhood vaccination. We used linear regression analyses and calculated GMC/T ratios (GMC/T in the high SES groups divided by GMC/T in the low SES groups) to assess the effect of educational level of the mother, net household income and the combination of both, on logarithmically transformed IgG concentrations for the different pathogens at the two timeframes after vaccination. A GMC/T ratio > 1 “favoured” high educational level or household income (that is, antibody concentrations were higher in the high SES group than the low SES group). Multivariable linear regression was performed to correct for migration background, sex and (exact) age at vaccination. We corrected for multiple testing by applying the Benjamini-Hochberg’s procedure on the p-values for the individual differences in GMC/T between low and high educational level, household income and the combination of both [17].

We compared the proportions of individuals with protective levels of IgG against the different pathogens between children from low-intermediate (hereafter: low) and high household income, and between children with mothers with low-intermediate (low) and high educational level [18-25].

The survey design of Pienter2 with five regions (strata) and 40 municipalities (clusters) was taken into account in all analyses by adding them as random effects, correcting the standard error of the estimates. The analyses were conducted in Stata version SE/15.1 (StataCorp LLC, Texas, USA).

Validation of results with Pienter1 data

We repeated the analyses with data from the Pienter1 study, which was conducted between October 1995 and December 1996 and covered data from 8,539 participants (response rate 56%).The Pienter1 study design was similar to Pienter2 and has been described elsewhere [26]. In Pienter1, only data on mother’s educational level (not on household income) was available. At the time of the Pienter1 study, vaccination with DTP-IPV started at 3 months of age (3, 4, 5, and 11 months) and only the whole cell pertussis vaccine was used. MenC vaccination was not yet part of the NIP. Antibody levels against diphtheria and tetanus were determined using toxin binding inhibition assays in Pienter1; antibodies against polio by neutralization tests, and antibodies against measles, mumps, rubella and Hib by ELISAs [27]. For pertussis, only antibodies against pertussis toxin were assessed in Pienter1 by ELISA.

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RESULTS

Study population

For the analyses by educational level, we included between 65 and 113 infants and children in the timeframe 1m-1y after vaccination per pathogen and between 141 and 232 infants and children in the timeframe 1-3y after vaccination per pathogen. For the analyses by net household income, these numbers were 46-101 and 117-191 respectively (Supplementary tables 1 and 2). Data on net household income were missing more often than data on educational level of the mother, which explains the difference in number of infants and children included. The characteristics of the study population are shown in tables 1 and 2. As expected, mother's educational level and net household income were correlated: infants and children of mothers with a low educational level were more often living in a family with a low net household income than infants and children of mothers with high educational level (table 1), and vice versa (table 2). There were significantly more children born outside the Netherlands in the low income and low educational level groups than in the high income and educational level groups.

GMC/T ratios

In figures 1 and 2, GMC/T ratios with 95% confidence intervals (CI) are presented for high versus low educational level of the mother and net household income respectively. A ratio >1 means that antibody levels are higher in children with high educational level of the mother or with high net household income, i.e. a ratio >1 favours a high level of SES. In the analysis by educational level of the mother (figure 1), the GMC/T ratio (and 95% CI) was >1 for Hib 1m-1y after vaccination (GMC/T ratio 2.99, 95% CI 1.42-6.30) and polio 2 virus 1m-1y after the 9-year booster vaccination (1.14, 1.01-1.27). In the analysis by net household income (figure 2), the GMC/T ratio was <1 for polio 1, 2 and 3 virus 1m-1y after the 11-month booster vaccination (polio 1: 0.74, 0.58-0.94; polio 2: 0.79, 0.64-0.97; polio 3: 0.72, 0.55-0.95) and for polio 3 virus also 1-3y after the 11-month booster vaccination (0.70, 0.56-0.88). In addition, the GMC ratio was <1 for pertussis prn ad ptx 1-3y after the 11-month booster vaccination (prn: 0.60, 0.37-0.98; ptx: 0.66, 0.47-0.95), for mumps 1-3 y after first vaccination (0.73, 0.55-0.97), and for rubella 1-3 y after first vaccination (0.70, 0.55-0.90) and 1m-1y after second vaccination (0.83, 0.55-0.90).

In the analysis by SES (educational level of the mother and net household income combined), the GMC/T ratios of rubella 1-3y after first vaccination and polio 3 virus 1-3y after the 11-month

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booster vaccination were <1 (rubella: 0.73, 0.55-0.97; polio 3: 0.68, 0.50-0.94; Supplementary figure 1). No other associations were found.

After correcting for sex, migration background and age at vaccination in multivariable linear regression analysis, the differences in GMC/T ratio by educational level remained only significant for Hib, 1m-1y after vaccination(3.88; 1.97-7.66) and polio 2, 1m-1y after the 9-year booster (1.15; 1.02-1.30), and by net household income for polio 1 and 3, 1m-1y after the 11-month booster dose (resp. 0.72; 0.58-0.91 and 0.73; 0.54-0.99) (Supplementary figures 2-7). In the multivariable regression analysis, some other differences became significant. In the analyses by educational level of the mother, the adjusted GMC/T ratio was 1.72 (1.07-2.76) for diphtheria 1m-1y after the 11-month booster vaccination, 1.36 (1.04-1.78) for tetanus and 1.23 (1.00-1.50) for polio 2 virus 1-3y after the 11-month booster vaccination.

After adjustment for multiple testing by applying the Benjamini-Hochberg's procedure, none of the differences in GMC/T between the high and low SES groups, neither in the univariable analyses nor in the multivariable analyses, were significant.

Proportions reaching protecting IgG levels

No differences were observed in proportions of infants and children reaching protective IgG levels with mothers of low versus high educational level, except for IgG levels against rubella. For rubella, 100% of infants of mothers with low educational level and 96% of infants of mothers with high educational levels reached IgG levels above the threshold for protection 1-3y after the first vaccination (p=0.02; table 3). In the analysis by net household income, 67% of infants from low income households and 50% of infants from high income households reached levels of protection against polio 3 virus 1-3 years after infant vaccination (p=0.04). The proportion of children with protective IgG levels against polio 3 is low in all children 1-3y after infant vaccination, but increases thereafter (table 3). This was also shown in previous studies using these data [28]. For the other pathogens, there were no significant differences in proportions of infants and children reaching protective IgG levels at the different timeframes. After adjustment for multiple testing, the differences between the high and low SES groups disappeared.

Validation of results with Pienter1 data

The analyses by educational level of the mother were repeated with Pienter1 data on 581 infants aged approximately 0-4 years and 494 children 4-12 years (a total of 1,075 children). None of the differences in IgG levels found between children of mothers from high versus low educational level in the Pienter2 study were also observed in the Pienter1 study. Three

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differences were found in the Pienter1 study that were not found in Pienter2: the GMC ratios and 95% CI were >1 for polio 1, 2 and 3 virus 1m-1y after the 11-month booster vaccination (resp. 1.43 (1.03-2.01); 1.46 (1.03-2.12); and 1.57 (1.04-2.34)). These differences remained significant after adjusting for age and sex (data not shown), but disappeared after adjustment for multiple testing.

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DISCUSSION

In this study, we explored the effect of two indicators of SES (educational level and net household income) on immune response to vaccination in infants and children vaccinated according to the Dutch NIP. No consistent patterns were observed that favoured either high or low SES for any of the studied pathogens at either timeframe (1 month to 1 year after vaccination and 1 to 3 years after vaccination). Although a few significant differences in GMC/T were found for some pathogens at some timeframes, these differences were not consistent over timeframes, nor observed after both infant and childhood vaccination. Moreover, repetition of the analyses with data from the Pienter1 serosurvey that was conducted ten years earlier did not show similar differences but rather a few other inconsistent differences. After adjusting for multiple testing, all significant differences disappeared, confirming the irrelevance of the few differences found in the individual comparisons. The proportion of infants and children with protective IgG levels against the different pathogens did not differ significantly between high and low SES, except for slight differences for rubella and polio 3.

Many factors may affect immune response to vaccination. Whereas there is strong evidence about the effect of intrinsic factors (such as age and genetics), comorbidity and vaccine factors on immune response to vaccination, the evidence about the relation with socioeconomic factors such as nutritional status and educational level is ambiguous [9]. Studying associations between SES and health is complicated since several mediators and moderators along the causal pathway should be considered [2]. Studies that explore the association between SES and health outcomes often use educational level, income and occupation as indicators of SES, not in the least because they are measurable and can be addressed in policies. Whereas education may impact health/lifestyle behaviour, it also affects income and occupation [29]. In our study, low educational level was indeed associated with low net household income. Household income and occupation affect healthcare seeking behaviour and lifestyle, but also influence living conditions (e.g. crowding) and the risk of exposure to hazardous factors including pathogens [2, 29]. For example, several studies have shown that low SES (expressed in factors such as sole-parent households, maternal education, car ownership) is associated with increased risk of acquiring pneumococcal, Hib and meningococcal disease in the community [30-32].

In a study in the Netherlands, weak associations were found between SES (educational level and income) and IgG concentrations induced by natural infections with rubella, measles, pneumococcus, Hib and MenC in non-vaccinated adults, although the direction of the association was not consistent (as in our study) [8]. In another study, higher IgG antibody levels

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against CMV were found in adults >25 years with lower education or income [33]. However, the relative contributions of differences in pathogen exposure versus differences in immune response after natural exposure, were difficult to assess in these studies.

Little is known to what extent SES affects humoral immunity independently of the risk of exposure. By looking at the immune response after vaccination, differences in exposure can be ruled out, at least for vaccine-preventable diseases that are no longer prevalent in the study population (such as rubella, diphtheria and polio in the Netherlands). Our results do not point towards a clinically significant impact of SES on humoral immunity to these vaccine-preventable diseases in Dutch children.

Our study had several strengths. First, we were able to use data from a national serosurvey in a representative sample of the Dutch population, including detailed and verified information on dates of vaccination for each included child [11]. Moreover; we were able to include children at two different timeframes after vaccination (1 month to 1 year, and 1-3 years). This allowed us to look at possible differences in the short versus medium-long term effects after vaccination. In addition, we were able to validate our results by repeating the analysis with data from the previous national serosurvey (10 years earlier) [26, 27].

The study also had some limitations. As proxies for SES, only mother's educational level and net household income were available from the Pienter2 study. Data on possible mediators and moderators between these indicators and immune response to vaccination, such as nutritional status, smoking and alcohol use, was not collected in the Pienter2 study. Hence, even if we had found a clear association between education/income and immune response, we would not have been able to interpret this in terms of causality; additional studies with another design would be needed for this.

Not for all children in the Pienter2 study, data was available on net household income. This resulted in smaller groups for the analysis by income and larger confidence intervals. Since people with a low income may be less eager to report on their income than people with higher incomes, the low income group may have been an underrepresentation of reality (selection bias). Due to small numbers in each group, we were not able to include more than two categories for education and net household income (low-intermediate versus high). By using two instead of several categories for educational level and income, we were not able to compare the highest versus the lowest levels of SES only, meaning that we might have missed differences only apparent when comparing the extremes. We compensated for this by also comparing GMC/T ratios in the low educational level *plus* low income group versus the high educational level *plus* high income group. However, in countries with relatively small differences

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in SES, such as the Netherlands, differences in immune response may be more difficult to detect.

Every child was sampled only once in this cross-sectional study, meaning that every child was included in only one timeframe after vaccination. Thus, the two timeframes (1m-1y and 1-3y) could not be compared directly as data in the two timeframes were from two different groups of children. On the other hand, within each timeframe the data were correlated (IgG levels against different pathogens measured in each sample). The latter implies that an outlier in IgG level against one pathogen would likely be an outlier in IgG levels against other pathogens as well if a general factor such as SES would be the cause of this. We did not verify this at the individual level.

Also, we aimed to look at immune response to vaccination only, interference with natural exposure to pathogens that are still circulating in the Netherlands (such as *Bordetella pertussis*, measles and mumps virus) could not be ruled out completely. Individuals who self-reported to have been diagnosed with clinical pertussis or mumps (resp. n=3 and n=0) were excluded from analysis, but we could not take into account possible natural boostering of immunity. In a previous study with Pienter2 data, an association was found between self-reported coughing > 2 weeks in the previous 12 months and higher pertussis ptx IgG levels [34]. Although we had access to this information, we decided not to exclude children of whom parents reported coughing > 2 weeks, since that would have meant that we had to exclude about 25% of our study population. However, there was no difference in the numbers of infants and children with > 2 weeks coughing between high and low SES.

Finally, we only considered the effect of SES on humoral immune response (IgG levels) to vaccination, which is still the most conventional response to investigate. However, vaccine response can also be quantified by looking at cellular and cytokine responses, and responses of the innate immune system [9]. Future studies should take this complex interplay of the different parts of the immune system into account.

In conclusion, this explorative study did not provide evidence for an association between SES and immune response to infant and childhood vaccination in the first three years after infant and childhood vaccination. Additional studies in other settings with data collected specifically for this purpose should confirm this. Moreover, it would be interesting to look at the longer term protection after vaccination in relation to SES.

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CONFLICTS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CONTRIBUTORS

JvdB, NR and MK designed the study and analysed the data. JvdB prepared the manuscript. All authors critically revised the manuscript. All authors approved the final article.

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473**TABLE 1.** Characteristics of all infants and children included in timeframes 1m-1y (n=358) and 1-3y (n=536) after vaccination
474according to NIP by educational level of mother

		Infants (approximately 0-4 years)					Children (approximately 4-12 years)				
		Low educational level		High educational level			Low educational level		High educational level		
		N	%	n	%	p-value	n	%	n	%	p-value
Total		190	53%	168	47%	-	327	61%	209	39%	-
Male sex		92	48%	89	53%	0.27	157	48%	103	49%	0.81
Born in the Netherlands		176	93%	157	93%	0.90	269	82%	189	90%	0.002
Migration background	**Indigenous Dutch**	123	65%	135	80%	0.002	199	61%	162	78%	0.004
	1st generation other western	0	0%	1	0.6%		1	0.3%	1	0.5%	
	2nd generation other western	4	2%	11	7%		12	4%	14	7%	
	1st generation Moroccan or Turkish	2	1%	1	0.6%		20	6%	2	1%	
	2nd generation Moroccan or Turkish	28	15%	1	0.6%		26	8%	1	0.5%	
	1st generation Surinam or Aruban or Dutch Antillean	4	2%	2	1%		16	5%	8	4%	
	2nd generation Surinam or Aruban or Dutch Antillean	16	8%	6	4%		23	7%	8	4%	
	1st generation other non-western	2	1%	3	2%		14	4%	8	4%	
	2nd generation other non-western	11	6%	8	5%		16	5%	5	2%	
Urbanization	**Very high**	35	18%	31	18%	0.97	58	18%	38	18%	0.96
	High	58	31%	54	32%		117	36%	71	34%	
	Moderate	35	18%	28	17%		65	20%	45	22%	
	Low	62	33%	55	33%		87	27%	55	26%	
Net household income	**High**	17	9%	73	43%	<0.001	29	9%	78	37%	<0.001
	Low	128	67%	71	42%		228	70%	101	48%	
	Unknown	45	24%	24	14%		70	21%	30	14%	
Median age (months) at vaccination (5th-95th	**DTP-IPV 11 m**	11 (10-13)		11 (10-13)		0.25	n.a.		n.a.		-
	DTP-IPV 4 y	n.a.		n.a.		-	46 (44-51)		46 (44-54)		0.11
	DT-IPV 9 y	n.a.		n.a.		-	107 (99-116)		107 (99-114)		0.98
	MMR1	14 (12-16)		14 (13-16)		0.63	n.a.		n.a.		-
	MMR2	n.a.		n.a.		-	107 (100-116)		107 (100-114)		0.96

percentile)	**MenC**	14 (14-16)	14 (14-16)	0.58	n.a.	n.a.	-
	Hib	11 (10-13)	11 (10-13)	0.059	n.a.	n.a.	-

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477**TABLE 2.** Characteristics of all infants and children included in timeframes 1m-1y (n=294) and 1-3y (n=438) after vaccination
478according to NIP by net household income

		Infants (approximately 0-4 years)					Children (approximately 4-12 years)				
		Low household income		High household income			Low household income		High household income		
		N	%	n	%	p-value	n	%	n	%	p-value
Total		203	69%	91	31%	-	331	75%	107	24%	-
Male sex		102	50%	48	53%	0.67	155	47%	55	51%	0.47
Born in the Netherlands		183	91%	86	95%	0.42	269	81%	100	93%	0.004
Migration background	**Indigenous Dutch**	122	60%	80	88%	0.02	192	58%	93	87%	0.007
	1st generation other western	0	0%	1	1%		1	0.3%	1	0.9%	
	2nd generation other western	10	5%	7	8%		16	5%	6	6%	
	1st generation Moroccan or Turkish	3	1%	0	0%		18	5%	0	0%	
	2nd generation Moroccan or Turkish	26	13%	0	0%		23	7%	0	0%	
	1st generation Surinam or Aruban or Dutch Antillean	6	3%	0	0%		18	5%	3	3%	
	2nd generation Surinam or Aruban or Dutch Antillean	18	9%	2	2%		25	8%	2	2%	
	1st generation other non-western	6	3%	0	0%		18	5%	2	2%	
	2nd generation other non-western	12	6%	1	1%		20	6%	0	0%	
Urbanization	**Very high**	42	21%	18	20%	0.51	63	19%	21	20%	0.75
	High	56	28%	35	38%		112	34%	43	40%	
	Moderate	39	19%	13	14%		68	21%	22	21%	
	Low	66	33%	91	31%		88	27%	21	20%	
Educational level mother	**High**	128	63%	17	19%	<0.001	101	31%	78	73%	<0.001
	Low	71	35%	73	80%		228	69%	29	27%	
	Unknown	4	2%	1	1%		2	1%	0	0%	
Median age (months) at vaccination (5th-95th percentile)	**DTP-IPV 11 m**	11 (10-13)		11 (10-13)		0.39	n.a.		n.a.		-
	DTP-IPV 4 y	n.a.		n.a.		-	46 (44-52)		46 (44-50)		0.55
	DT-IPV 9 y	n.a.		n.a.		-	107 (99-114)		107 (100-114)		0.89
	MMR1	14 (14-16)		14 (13-16)		0.81	n.a.		n.a.		-
	MMR2	n.a.		n.a.		-	107 (100-115)		107 (100-114)		0.39
	MenC	14 (14-16)		14 (14-16)		0.89	n.a.		n.a.		-

	Hib	11 (10-13)	11 (10-13)	0.17	n.a.	n.a.	-

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481**TABLE 3.** Comparison of proportions of infants and children with protective IgG levels by educational level of mother and net
482household income

			Educational level of mother					Net household income				
			Low educational level		High educational level			Low household income		High household income		
Pathogen	**Threshold for protection** [17-24]	**Vaccination**	**n/N**	**%**	**n/N**	**%**	**p-value**	**n/N**	**%**	**n/N**	**%**	**p-value**
Measles	≥0.2 IU/ml	BMR1, 1m-1y	42/43	98%	41/41	100%	0.31	38/39	97%	27/27	100%	0.42
		BMR1, 1-3y	126/126	100%	102/103	100%	0.28	135/135	100%	54/54	100%	-
		BMR2, 1m-1y	62/62	100%	25/25	100%	-	56/56	100%	13/13	100%	-
		BMR2, 1-3 y	86/86	100%	68/69	99%	0.25	88/88	100%	30/30	100%	-
Mumps	≥45 RU/ml	BMR1, 1m-1y	40/43	93%	36/41	88%	0.42	37/39	95%	24/27	89%	0.36
		BMR1, 1-3y	112/126	89%	88/103	85%	0.48	121/135	90%	46/54	85%	0.24
		BMR2, 1m-1y	60/62	97%	25/25	100%	0.37	55/56	98%	12/13	92%	0.26
		BMR2, 1-3 y	84/86	98%	68/69	99%	0.71	86/88	98%	30/30	100%	0.39
Rubella	≥10 IU/ml	BMR1, 1m-1y	43/43	100%	41/41	100%	-	39/39	100%	27/27	100%	-
		BMR1, 1-3y	126/126	100%	99/103	96%	0.02	134/135	99%	53/54	98%	0.49
		BMR2, 1m-1y	61/62	98%	25/25	100%	0.54	55/56	98%	13/13	100%	0.53
		BMR2, 1-3 y	85/86	99%	67/69	97%	0.45	87/88	99%	29/30	97%	0.41
Diphtheria	≥0.01 IU/ml	DTP-IPV 11 m, 1m-1y	38/40	95%	48/48	100%	0.09	43/45	96%	28/28	100%	0.19
		DTP-IPV 11 m, 1-3y	108/119	91%	78/88	89%	0.61	108/122	89%	39/44	89%	0.98
		DTP-IPV 4 y, 1m-1y	70/70	100%	43/43	100%	-	75/75	100%	26/26	100%	-
		DTP-IPV 4 y, 1-3y	95/96	99%	66/67	99%	0.79	98/98	100%	35/36	97%	0.13

		DT-IPV 9 y, 1m-1y	53/53	100%	24/24	100%	-	48/48	100%	12/12	100%	-
		DT-IPV 9 y, 1-3y	83/83	100%	68/68	100%	-	87/87	100%	30/30	100%	-
Tetanus	≥0.01 IU/ml	DTP-IPV 11 m, 1m-1y	40/40	100%	48/48	100%	-	45/45	100%	28/28	100%	-
		DTP-IPV 11 m, 1-3y	119/119	100%	88/88	100%	-	122/122	100%	44/44	100%	-
		DTP-IPV 4 y, 1m-1y	69/69	100%	43/43	100%	-	75/75	100%	26/26	100%	-
		DTP-IPV 4 y, 1-3y	95/95	100%	67/67	100%	-	98/98	100%	35/35	100%	-
		DT-IPV 9 y, 1m-1y	53/53	100%	24/24	100%	-	48/48	100%	12/12	100%	-
		DT-IPV 9 y, 1-3y	83/83	100%	68/68	100%	-	87/87	100%	30/30	100%	-
Polio 1	Log^2≥3	DTP-IPV 11 m, 1m-1y	39/40	98%	47/48	98%	0.90	44/45	98%	27/28	96%	0.73
		DTP-IPV 11 m, 1-3y	107/119	90%	82/88	93%	0.50	113/122	93%	39/44	89%	0.35
		DTP-IPV 4 y, 1m-1y	70/70	100%	43/43	100%	-	75/75	100%	26/26	100%	-
		DTP-IPV 4 y, 1-3y	94/96	98%	66/67	99%	0.78	95/98	97%	36/36	100%	0.37
		DT-IPV 9 y, 1m-1y	53/53	100%	24/24	100%	-	48/48	100%	12/12	100%	-
		DT-IPV 9 y, 1-3y	82/83	99%	69/69	100%	0.36	87/87	100%	30/30	100%	-
Polio 2	Log^2≥3	DTP-IPV 11 m, 1m-1y	40/40	100%	47/48	98%	0.36	45/45	100%	27/28	96%	0.21
		DTP-IPV 11 m, 1-3y	101/119	85%	80/88	91%	0.26	106/122	87%	39/44	89%	0.72
		DTP-IPV 4 y, 1m-1y	70/70	100%	42/43	98%	0.16	75/75	100%	25/26	96%	0.06
		DTP-IPV 4 y, 1-3y	95/96	99%	67/67	100%	0.42	98/98	100%	35/36	97%	0.13
		DT-IPV 9 y, 1m-1y	53/53	100%	24/24	100%	-	48/48	100%	12/12	100%	-
		DT-IPV 9 y, 1-3y	82/83	99%	69/69	100%	0.36	87/87	100%	30/30	100%	-
Polio 3	Log^2≥3	DTP-IPV 11 m, 1m-1y	38/40	95%	44/48	92%	0.56	44/45	98%	24/28	86%	0.06
		DTP-IPV 11 m, 1-3y	77/119	65%	49/88	56%	0.27	82/122	67%	22/44	50%	0.04
		DTP-IPV 4 y, 1m-	64/70	91%	35/43	81%	0.19	67/75	89%	22/26	85%	0.51

		1y										
		DTP-IPV 4 y, 1-3y	78/96	81%	52/67	78%	0.57	79/98	81%	28/36	78%	0.75
		DT-IPV 9 y, 1m-1y	53/53	100%	23/24	96%	0.16	48/48	100%	12/12	100%	-
		DT-IPV 9 y, 1-3y	79/83	95%	67/69	97%	0.57	85/87	98%	28/30	93%	0.28
Pertussis-prn	≥25 EU/ml	DTP-IPV 11 m, 1m-1y	24/29	83%	30/36	83%	0.95	31/35	89%	13/18	72%	0.15
		DTP-IPV 11 m, 1-3y	15/110	14%	14/85	16%	0.60	19/112	17%	5/42	12%	0.43
		DTP-IPV 4 y, 1m-1y	42/69	61%	31/45	69%	0.35	44/74	59%	19/25	76%	0.05
		DTP-IPV 4 y, 1-3y	43/88	49%	29/53	55%	0.55	47/86	55%	14/31	45%	0.51
Hib	≥0.15 µg/ml	Hib 1m-1y	34/39	87%	46/48	96%	0.19	40/45	89%	27/28	96%	0.27
		Hib 1-3y	96/116	83%	84/93	90%	0.13	100/117	85%	43/49	88%	0.72
MenC	≥2 µg/ml	MenC 1m-1y	23/43	53%	22/42	52%	0.91	24/41	59%	14/26	54%	0.66
		MenC 1-3y	18/130	14%	11/102	11%	0.45	20/135	15%	4/56	7%	0.14

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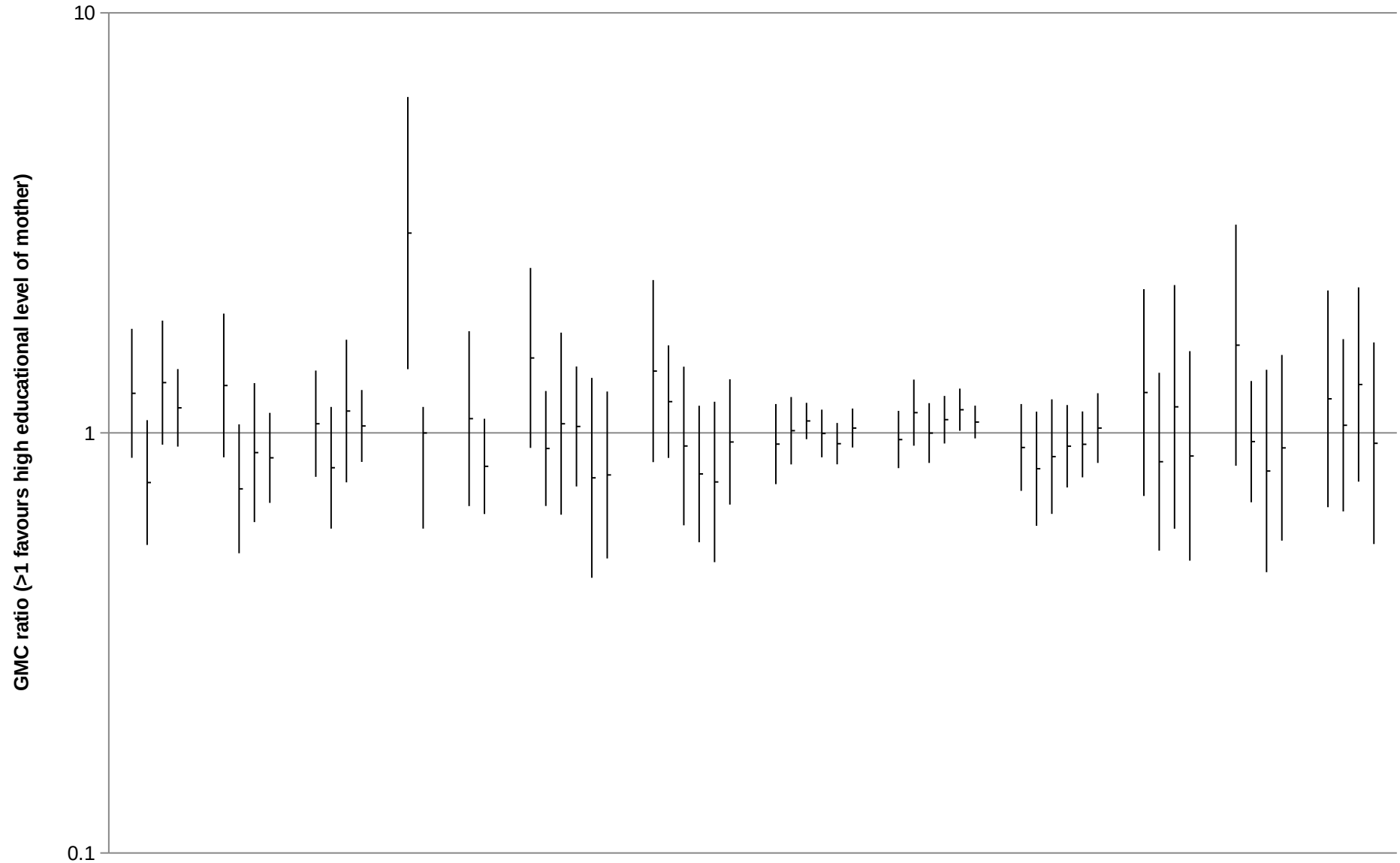
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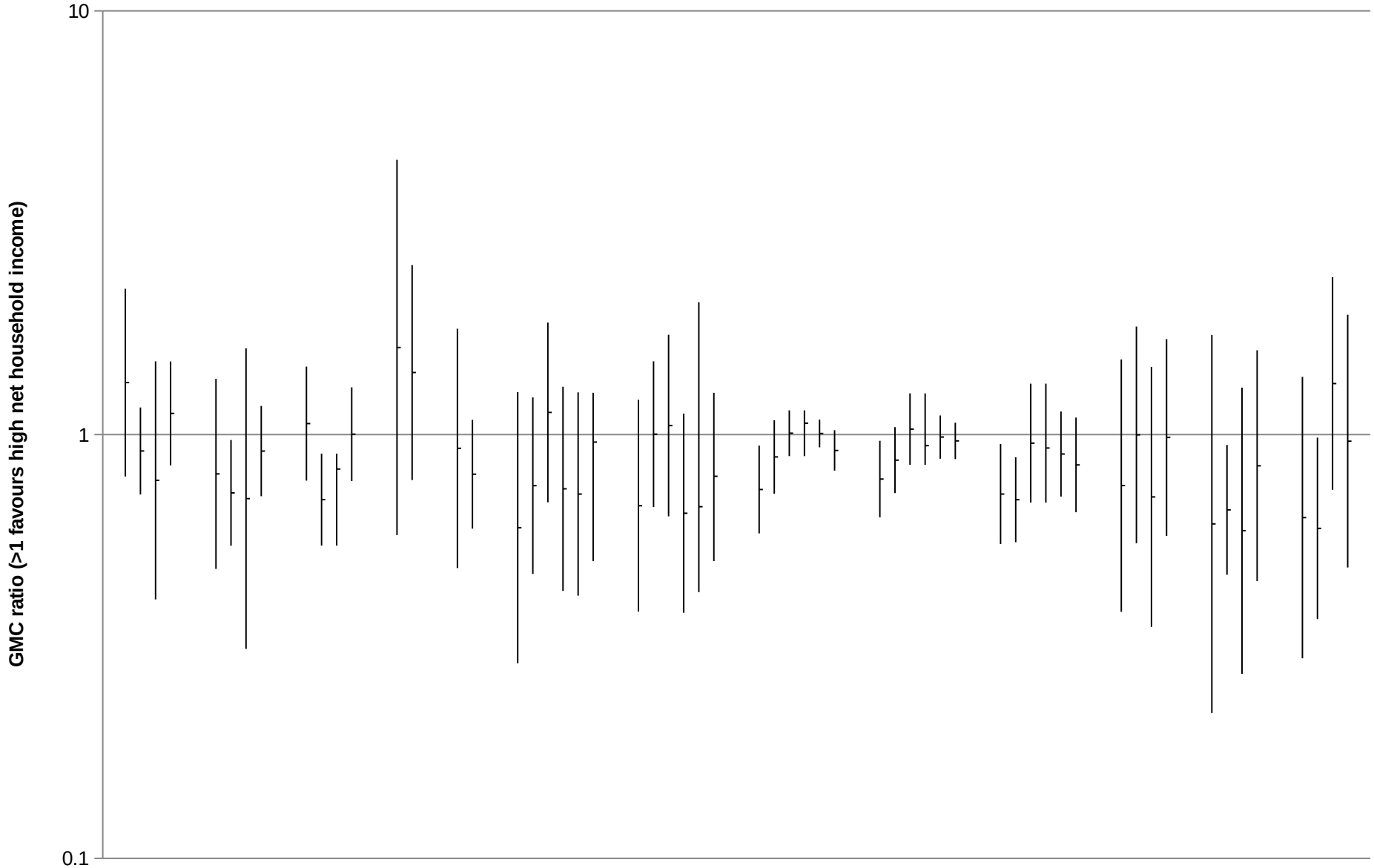
GMC ratio (>1 favours high educational level of mother)

FIGURE 1. GMC/T ratios: high versus low educational level of mother, with 95% confidence intervals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GMC ratio (>1 favours high net household income)

FIGURE 2. GMC ratios: high versus intermediate/low net household income, with 95% confidence intervals

SUPPLEMENTARY TABLE 1. Number of infants and children included by educational level of mother

SUPPLEMENTARY TABLE 2. Number of infants and children included by net household income

SUPPLEMENTARY FIGURE 1. GMC/T ratios: high versus low SES total (net household income and educational level combined), with 95% confidence intervals

SUPPLEMENTARY FIGURE 2. GMC/T ratios: high versus low educational of mother with 95% confidence intervals, unadjusted (red square) and adjusted (blue circle), MMR

SUPPLEMENTARY FIGURE 3. GMC/T ratios: high versus low educational of mother with 95% confidence intervals, unadjusted (red squares) and adjusted (red circles), Hib and MenC

SUPPLEMENTARY FIGURE 4. GMC/T ratios: high versus low educational of mother with 95% confidence intervals, unadjusted (red squares) and adjusted (blue circles), DTP-IPV

SUPPLEMENTARY FIGURE 5. GMC/T ratios: high versus low net household income with 95% confidence intervals, unadjusted (red squares) and adjusted (blue circles), MMR

SUPPLEMENTARY FIGURE 6. GMC/T ratios: high versus intermediate/low net household income with 95% confidence intervals, unadjusted (red squares) and adjusted (blue circles), Hib and MenC

SUPPLEMENTARY FIGURE 7. GMC/T ratios: high versus intermediate/low net household income with 95% confidence intervals, unadjusted (red squares) and adjusted (blue circles), DTP-IPV